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# Mortality in Patients With Acute Intermittent Porphyria Requiring Hospitalization: A United States Case Series

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**Acute intermittent porphyria (AIP) is a genetic disorder in which patients may have life threatening attacks of neurologic dysfunction. This study examined the prognosis during the past 50 years of patients in the United States who required hospitalization for porphyric attacks.**

**The cumulative survival was determined for 136 patients with AIP who were hospitalized for porphyric attacks between 1940 and 1988. Diagnosis was established on the basis of clinical symptoms, in combination with increased urinary excretion of porphobilinogen. The patient group had an average age of 32 years (range 9 to 75) at diagnosis and consisted of 43 males and 93 females. At follow-up, 19 males (44%) and 31 females (33%) were deceased.**

**The standardized mortality ratio for the 136 patients, compared to an age-matched hypothetical population experiencing USA 1970 Census Death Rates was 3.2, with a 95% confidence interval of 2.4–4.0. Most deaths occurred during the initial porphyric attack (20% of deaths) or a subsequent attack (38% of deaths). Suicide was also common (five deaths). Comparison was made between 50 patients who were diagnosed before 1971, the year in which hematin therapy became available, and 86 patients who were diagnosed afterward. There was improved survival in the latter group, particularly after 10 years from the time of diagnosis, but this did not reach statistical significance.**

**In conclusion, the proportionate increase in mortality due to symptomatic AIP was three-fold compared to the general population during the past 50 years. The major cause of the increased mortality was the porphyric attack itself.** © 1996 Wiley-Liss, Inc.

**KEY WORDS: acute intermittent porphyria, porphyric attack, mortality, prognosis, hematin**

## INTRODUCTION

The introduction of Sulfonal to the pharmaceutical market in 1888 ushered in a mysterious new illness. Stokvis reported the case of a drug addict who passed urine the color of port wine and died after ingesting this medicine, providing the first clinical record of the porphyric attack [With, 1980]. During the next century several publications described the clinical and biochemical features of this disorder [Schmid et al., 1954; Goldberg, 1959; Stein and Tschudy, 1970; Mustajoki, 1986; Bloomer and Bonkovsky, 1989; Kappas et al., 1995].

Acute intermittent porphyria (AIP) is the most common cause of the porphyric attack in the United States. AIP is a metabolic disorder, inherited as an autosomal dominant trait, that is caused by a defect in the gene which codes for the third enzyme of the heme biosynthetic pathway, porphobilinogen (PBG) deaminase [Strand et al., 1970; Anderson et al., 1981; Llewellyn et al., 1987; Delfau et al., 1990]. Patients also have a marked increase in hepatic delta-aminolevulinic acid (ALA) synthase activity, which is the first and rate limiting step in hepatic heme biosynthesis, during symptomatic periods [Strand et al., 1970; Tschudy et al., 1965]. As a result, PBG and ALA are excreted in excess amounts in the urine.

The clinical manifestation of AIP is attacks of neurologic dysfunction [Bonkovsky and Schady, 1982]. Patients have no cutaneous manifestations. The attacks typically begin with abdominal pain which may be followed rapidly by the development of a peripheral neuropathy. Involvement of the central nervous system manifests as mental confusion, hallucination, and depression. Seizures and frank coma also occur. The pathogenesis of the neurological involvement in AIP

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has yet to be precisely defined. The most likely possibilities are that ALA acts as a neurotoxin, that heme deficiency affects the nervous system adversely, or a combination of the two [Bonkovsky and Schady, 1982].

It is important for patients with AIP to avoid the use of drugs and other conditions which precipitate acute attacks [Bonkovsky and Schady, 1982]. When attacks occur, they are managed with a high carbohydrate diet and the intravenous administration of heme (hematin) [Bonkovsky et al., 1976, 1971; Lamon et al., 1979; Pierach et al., 1980; Mustajoki et al., 1989]. These therapies have been shown in both experimental and clinical studies to repress the induction of hepatic ALA synthase activity [Bonkovsky et al., 1979].

In contrast to the information available on the clinical and biochemical features of AIP, no studies in the United States have assessed the long-term prognosis in patients who have experienced acute attacks. In this study we examined the mortality rate from symptomatic AIP in the United States over the past 50 years.

## MATERIALS AND METHODS

### Patient Population

The study population was composed of patients with symptomatic AIP who were diagnosed by the Watson Laboratory between the years 1940 and 1988. The diagnosis was established on the basis of symptoms compatible with an acute porphyric attack in combination with increased urinary excretion of porphobilinogen (Table I). All of the patients had abdominal pain, often accompanied by other signs and symptoms of neurologic dysfunction (Table II). None of the patients had cutaneous manifestations. The patients required hospitalization for management of their attacks.

A total of 168 patients with symptomatic AIP was available for the study, and follow-up information was obtained on 136 (81%) (Table I). Twenty-six of these patients were evaluated and managed directly by physicians associated with the Watson Laboratory. The remainder were cared for by physicians in their own communities throughout the United States. Except for two patients aged 9 and 10 years, all of the patients were 14 years or older at the time of diagnosis. The 9-year-old patient was diagnosed on the basis of reduced erythrocyte PBG deaminase activity prior to developing symptoms. The 10-year-old patient had received anti-epileptic medicines since age 8 months for mental retardation and seizures, and this was felt to have precipitated porphyric symptoms. Follow-up information was obtained through review of hospital records in 56, questionnaires sent to the patients' physicians in 50, and questionnaires sent to the patients or their families in 30. The 32 patients on whom follow-up information could not be obtained did not differ from the study population with respect to age at diagnosis, gender, biochemical abnormalities, or clinical manifestations. Approval for the study was obtained from the Human Investigation Committee at the University of Minnesota.

### Chemical Analyses

Early measurements of urinary excretion of PBG were made in units per day, with conversion to mg per day when the method of Mauzerall and Granick [1956] became available [Bossenmaier and Cardinal, 1968]. The early measurements were converted to mg per day based on the relationship established in the Watson Laboratory between units and mg. In 64 patients erythrocyte PBG deaminase activity was measured by modifications of the method described by Sassa et al. [1974].

### Statistical Analysis

Data obtained from the 136 patients were compiled and stored in EXCEL database. These data were used to generate survival curves and calculate the standardized mortality ratio compared to a hypothetical population experiencing USA 1970 census death rates [Kelsey et al., 1986]. The 1970 mortality data was selected as it is based on the decennial USA census closest to the middle of the follow-up period for the AIP patients and would be more accurate than mortality rates based on inter-census interpolation of the size of the population within each age strata. The standardized mortality ratio is the ratio of the number of deaths observed among the patients with symptomatic AIP compared to the number of expected deaths as calculated from the 1970 death rates. Comparisons between patients were made by chi-square analysis, Fisher's Exact Test, log rank test to compare survival curves, or t-tests depending on the type of data.

TABLE I. Patient Population With Symptomatic Acute Intermittent Porphyria

| | Males | Females | All patients |
|---|---|---|---|
| Number | 43 | 93 | 136 |
| Age at diagnosis (yrs)[a] | 34 (9–75) | 32 (14–64) | 32 (9–75) |
| Urinary PBG (mg/day)[b] | 67 (7–782) | 62 (4.1–350) | 65 (4.1–782) |
| Urinary ALA (mg/day)[b] | 31 (4–203) | 21 (1–110) | 22 (1–203) |
| Erythrocyte PBG deaminase (units)[a] | 17 (11–24) | 19 (12–28) | 18 (11–38) |
| Deceased at follow-up | 19 | 31 | 50 |

[a] Numbers are mean (range); normal range for erythrocyte PBG deaminase activity is 20.9 to 42.4 nmol uroporphyrin/ml RBC/hr (units).
[b] Numbers are median (range); normal range for urinary porphobilinogen (PBG) and urinary aminolevulinic acid (ALA) excretion is 0 to 4 mg/day.

TABLE II. Complications in Patient Population

| | Alive at follow-up | Dead at follow-up |
|---|---|---|
| Number | 86 | 50 |
| Males | 24 | 19 |
| Females | 62 | 31 |
| Age at diagnosis (yrs)[a] | 30 ± 9.9 | 35 ± 14.0 |
| Age at death or follow-up[a] | 44 ± 13.7 | 44 ± 19.7 |
| Peripheral neuropathy: | | |
| Yes | 58 | 41 |
| No | 23 | 7 |
| Unknown | 5 | 2 |
| Seizures: | | |
| Yes | 22 | 21 |
| No | 61 | 27 |
| Unknown | 3 | 2 |
| Hypertension:[b] | | |
| Yes | 41 | 31 |
| No | 33 | 11 |
| Unknown | 12 | 8 |
| Azotemia:[c] | | |
| Yes | 25 | 28 |
| No | 44 | 11 |
| Unknown | 17 | 11 |

[a] Numbers are mean ± SD.
[b] Systolic blood pressure > 140 and/or diastolic blood pressure > 90.
[c] BUN > 25 mg/dL.

## RESULTS

The standardized mortality ratio for the 136 patients with symptomatic AIP was 3.2 with a 95% confidence interval of 2.4–4.0 (Fig. 1). When the ten patients who died during the initial attack were excluded from the analysis, the standardized mortality ratio remained significantly increased (2.6 with a 95% confidence interval of 1.8–3.4). Recurrent attacks were experienced by 109 patients. When the 86 patients who were alive at follow-up were compared with the 50 who had died, no significant difference was found as to the age at diagnosis (Table II). The frequency of complications which occurred during acute porphyric attacks was increased in patients who had died compared to those still living, but only the presence of azotemia was of statistical significance ($P < 0.05$ by chi-square analysis) (Table II). This significance remained when patients who died during their initial attack were excluded from the comparison. There were no significant differences in the levels of urinary ALA and PBG between the two groups.

The survival curve for the 50 patients diagnosed before 1971, the year in which hematin became available for treating acute porphyric attacks, was compared to that for the 86 patients diagnosed during or after 1971. There was improved survival in the latter group, particularly after 10 years from the time of diagnosis, but this did not reach statistical significance by the log rank test (Fig. 2). A total of 71 patients received hematin for management of porphyric attacks.

The majority of the 50 deaths occurred during the initial attack (20% of deaths) or a subsequent attack (38% of deaths) (Table III). Of the 12 patients diagnosed after 1971 who died during a porphyric attack, 11 were receiving hematin therapy. All of these patients were in an advanced attack before hematin was administered, with 10 requiring mechanical ventilation because of paralysis. None of the patients diagnosed before 1971 who died during a porphyric attack were receiving hematin. Complications from respiratory paralysis were the leading causes of death in the porphyric attack. Suicide was the cause of death in 5 patients, a rate of 3.7% compared to an expected rate of 0.01% for the general population. There were no deaths due to hepatocellular carcinoma. No differences in the causes of death were noted between males and females.

## DISCUSSION

Although considerable information has been generated about the clinical and biochemical features of AIP, there is little published information regarding the life expectancy of patients with this disorder. Studies uti-

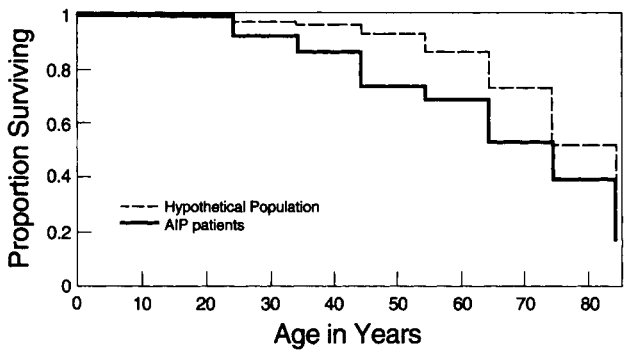


Fig. 1. The cumulative survival, in 10 year intervals, of 136 patients with symptomatic acute intermittent porphyria (AIP) is compared with that of a hypothetical population experiencing 1970 USA census death rates. Since the youngest AIP patient was 9 years old at the time of diagnosis, both populations were assumed to have 100% survival at 5 years of age. The standardized mortality ratio for the AIP patients compared to the hypothetical population was 3.2, with a 95% confidence interval of 2.4 to 4.0.

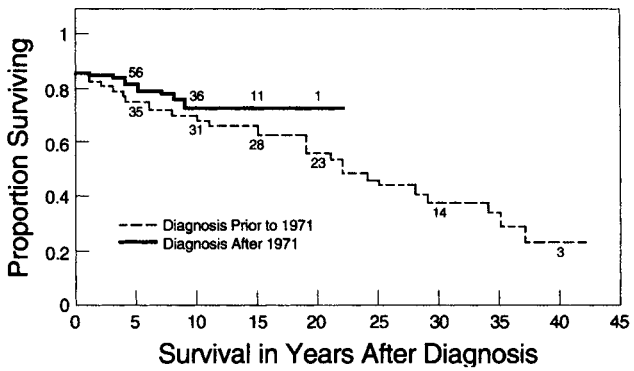


Fig. 2. The cumulative survival of 50 patients with symptomatic acute intermittent porphyria who were diagnosed before 1971, the year in which hematin therapy became available, is compared with that of 86 patients diagnosed during or after 1971. The survival curves begin at the time of diagnosis. The numbers on the curves indicate the number of patients still being followed at that time interval. These curves do not differ significantly by the log rank test.

TABLE III. Causes of Death in Patient Population

| | Diagnosed before 1971 | Diagnosed after 1971 |
|---|---|---|
| Number | 50 | 86 |
| Number deceased | 30 | 20 |
| Died in first attack | 4 | 6 |
| Died in subsequent attack | 13 | 6 |
| Suicide | 2 | 3 |
| Miscellaneous cause of death | 11[a] | 5[b] |

[a] Cardiac event, 5; unknown, 3; leukemia,1; cerebrovascular accident, 1; renal failure, 1.
[b] Cardiac event, 1; unknown, 2; cancer, 1; grand mal seizure, 1.

lizing the measurement of erythrocyte PBG deaminase activity to identify patients with the gene defect for AIP have shown that the majority of patients never develop clinical manifestations [Bottomley et al., 1981; Pierach et al., 1987]. These patients, who are considered to be silent carriers of the gene defect, appear to have a normal life span. Patients with symptomatic disease, on the other hand, are believed to have a poor prognosis compared to the general population, although this has never been quantified in the United States. We utilized the AIP database in the Watson Laboratory, dating back to 1940, to pursue follow-up on a group of symptomatic patients who had required hospitalization for porphyric attacks.

In a patient population of 136 we found a three-fold increase in the mortality rate as compared with the general population. The majority of deaths occurred during the first porphyric attack or during a subsequent attack (58% of all deaths). Suicide was also a major cause of death, occurring at a rate 370 times that expected in the general population. The high suicide rate likely reflects the psychiatric symptoms and/or chronic pain syndrome which may be caused by AIP [Bonkovsky and Schady, 1982]. None of the deaths was due to hepatocellular carcinoma, in contrast to the high frequency of this cancer in Scandinavian patients with AIP [Lithner and Wetterberg, 1984; Kauppinen and Mustajoki, 1988].

The frequency of clinical manifestations in our patients was similar to that cited by Bonkovsky and Schady [1982] for patients with AIP who require hospitalization. Of the different complications associated with AIP, only azotemia was found to be significantly associated with mortality (Table II). Azotemia during the porphyric attack has been attributed primarily to a reduction in the intravascular volume [Goldberg, 1959; Stein and Tschudy, 1970; Bloomer et al., 1971].

Previous studies of mortality in AIP examined a smaller series of patients and did not compare the rate to the general population. Beattie and Goldberg [1976] reported that 12 of 50 patients in the United Kingdom died during the initial attack. The survival rate of the group 20 years after the initial attack was 57%. A study of 42 symptomatic patients in the United States over a 13-year period documented a fatality rate of 10% due to acute attacks [Stein and Tschudy, 1970]. A follow-up study was not carried out in this group in order to determine long-term mortality, however.

Recent studies in Finland by Kauppinen and Mustajoki [1993] indicated that the prognosis for patients with AIP improved over the past 20 years. The improved prognosis was attributed to several factors, including earlier detection of the disease due to the increased awareness of physicians and better diagnostic facilities, as well as improved treatment of the acute attack. Our data support this finding (Fig. 2), but longer follow-up is necessary to be certain.

It is likely that hematin therapy has improved the prognosis of patients experiencing an acute porphyric attack [Mustajoki and Nordmann, 1993]. Previous studies have demonstrated the efficacy of hematin, but generally used patients as their own controls, initiating therapy after the patients failed to respond clinically and biochemically to a high carbohydrate intake [Lamon et al., 1979; Pierach et al., 1980; Mustajoki et al., 1989]. The one controlled study failed to show a significant benefit of heme administration on resolution of the clinical manifestations of the attack, although the number of patients studied was too small to reach a definitive conclusion [Herrick et al., 1989].

It is notable that 11 patients in our study who were diagnosed after 1971 died during an attack despite receiving hematin (Table III). All of these patients were in an advanced attack before hematin was administered, and it has been shown that hematin is more effective when used early during an attack before fixed nerve damage has occurred [Lamon et al., 1979; Mustajoki and Nordmann, 1993]. This emphasizes the importance of identifying carriers of the gene defect for AIP at an early age, so that they can be counseled to avoid factors which precipitate attacks, and so that therapy can be given promptly in the event an attack occurs.

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